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EXAMINER	
PARAS JR, PETER	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/507,268	YLA-HERTTUALA ET AL.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/9/2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *14-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10142004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-19 are pending.

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I claim(s) 1-13 drawn to a baculovirus vector having a modified capsid and a method for delivering a peptide into the nucleus of a cell.

Group II, claim(s) 14-19, drawn to a method for selecting a target gene.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature linking the inventions of Groups I-II appears to be a modified baculovirus expressing heterologous peptides. However, Grabherr et al (Biotechniques, 1997, 22: 730-735; IDS) taught a modified baculovirus comprising a fusion of gp64-HIV-1 gp41.

Accordingly, a special technical feature, in light of the teachings of Grabherr et al, does not link Groups I-II.

During a telephone conversation with David Saliwanchik on 12/12/05 a provisional election was made without traverse to prosecute the invention of Group I, claims 1-13. Affirmation of this election must be made by applicant in replying to this Office action. Claims 14-19 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

The disclosure is objected to because of the following informalities: the instant application is not in compliance with the sequence rules (see below).

Appropriate correction is required. Failure to comply with the sequence rules will be considered non-responsive

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) as follows: The specification is replete with unidentified nucleic acid sequences.

Applicant must provide the following to be in compliance with the sequence rules: 1) an initial or substitute computer readable form (CRF) copy of the sequence listing; 2) an initial or substitute paper copy of the sequence listing, as well as an amendment directing its entry into the specification; 3) a statement that the content of the paper and computer readable copies are the same and, where applicable include no new matter, as required by 37 CFR 1.821 (e), 1.821 (f), 1.821 (g), 1.825 (b) or 1.825 (d); and 4) an amendment to the specification to include an appropriate sequence identifier that properly identifies each sequence in the specification.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the following: 1) a baculovirus comprising a vp39-green fluorescent protein fusion, wherein the fusion protein is expressed on the surface of the baculovirus capsid; and 2) an *in vitro* method for delivering a peptide into the nucleus of a eukaryotic cell comprising contacting the cell with a baculovirus comprising a vp39-green fluorescent protein fusion does not reasonably provide enablement for the other baculoviruses and methods embraced by the claims. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a baculovirus comprising a modified capsid protein, wherein the modified protein is vp39, p24 or p80. The claims are further directed to methods for delivering a peptide into the nucleus of a cell comprising contacting the cell with the same baculovirus.

The specification discusses that the invention features a baculovirus comprising a modified capsid protein. The specification further discusses that such a baculovirus could be used for delivering a peptide to the nucleus of a cell, for therapeutic benefit or for studying nuclear transport of the baculovirus capsid. See the specification at page 4, at lines 5-12, and also at page 5, at lines 17-28. While the specification provides extensive teachings pertaining to creation of a baculovirus comprising a modified vp39 capsid protein, wherein the modified vp39 comprises a fusion of vp39 and green fluorescent protein (GFP), and wherein the fusion protein is expressed on the surface of the baculovirus capsid, the specification fails to provide any relevant teachings or specific guidance with regard to creation of the other baculoviruses that display heterologous proteins on their capsids as embraced by the claims. Also, the specification has provided guidance for in vitro methods of delivering a peptide into the nucleus of a eukaryotic cell but has failed to provide guidance or working examples correlating to in vivo delivery of a peptide into the nucleus of a eukaryotic cell. Given the lack of guidance provided by the specification it would have required undue experimentation to make and use the invention as claimed.

As a first issue, the claims are broadly directed to baculoviruses that display and/or express heterologous peptides on/in their capsids. The specification has provided extensive guidance and working examples, which relate to modifying capsid protein vp39 to create a vp39-GFP fusion protein that is expressed on the capsid surface of a baculovirus. The specification however has not provided guidance for modifying other proteins to such that heterologous proteins are displayed on the capsid surface. Vp 39 is expressed on the capsid surface such that a vp39 fusion protein, for example a vp39-gfp fusion, is also expressed on the capsid surface. See Kukkonen et al (Molecular Therapy, 2003, 8(5): 853-862) on page 855 in figure 3. The specification has contemplated that for delivery of heterologous peptides to the nucleus of a eukaryotic cell, the heterologous peptides must be expressed on the baculovirus capsid surface. While it is clear that vp39 is expressed on the capsid surface, the specification has failed to provide guidance with respect to which other proteins are displayed or expressed on the capsid surface. The term "displayed" implies that the goal of the invention is to express heterologous peptides on the surface of the baculovirus capsid. However, given the lack of guidance provided by the specification with respect to which proteins are expressed on the capsid surface, it is unpredictable if the other proteins embraced by the claims are expressed on the capsid surface. For example, the specification has failed to provide any relevant teachings with respect to the capsid location of p24 and p80 expression. Kukkonen et al has taught that the surface of the baculovirus capsid is composed primarily of vp39. Moreover, even if p24 and p80 are expressed on the capsid surface at a level comparable to vp39, it is not apparent from

the lack of guidance provided by the specification if any of vp39, p24, or p80 are expressed at a level sufficient to present an adequate amount of heterologous peptide in a eukaryotic nucleus that results in an effect of any kind, particularly a therapeutic effect as has been purported by the specification. Given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the art to make and use the invention as claimed without a reasonable expectation of success.

As a final issue, claims 10-13 are directed to a method for delivering a peptide into the nucleus of a cell. First, claim 13 requires the cell to be *E. coli.* It is well known that prokaryotic cells do not comprise a defined nucleus. Therefore, it is unpredictable if a peptide could be transported to the nucleus of a prokaryotic cell, such as *E. coli.* Next, the specification has taught that baculoviruses are unpredictable with respect to transduction of mammalian cells due to a transport block between the cytosol and the nucleus. For example, see page 10 of the specification. Moreover, the state of the art as evidenced by Kukkonen et al reported that a vp39-egfp baculovirus did not enter the nucleus of human cells (EAHY, MG63 and NHO) but was able to enter the nucleus of Pk1 pig cells. See page 856, in column 2, in the discussion section. The observations of Kukkonen et al support the unpredictable nature of mammalian cell transduction by baculoviruses. Kukkonen et al went to characterize baculovirus entry and release of viral capsid into mammalian cells as general phenomena. Finally, Kukkonen et al discussed the difficulties of target cell transduction, which include internalization, escape from endosome and transport of the genetic material to the nucleus. While

transduction can be improved by selection of cell membrane targeting moieties, routing from the cytosol to the nucleus remains difficult to achieve. See Kukkonen et al at page 857, in column 2. In light of the above, the specification has failed to provide guidance to overcome the unpredictability of transducing cells with a baculovirus, particularly cells *in vivo* for therapeutic benefit resulting from delivery of a peptide. Given the lack of guidance provided by the specification it would have required undue experimentation to make and use the invention as claimed without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for displaying heterologous peptides on the capsid of a baculovirus, the lack of direction or guidance provided by the specification correlating to modifying the capsid of a baculovirus, the absence of working examples for the demonstration or correlation to delivery of a peptide to the nucleus of a cell, the unpredictable state of the art with respect nuclear delivery of a peptide via a baculovirus, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 and 10-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Liu et al (Acta Virolgica, 2000, 44: 157-161).

The claims are directed to a baculovirus having a modified capsid or genome, wherein vp39, p24 or p80 is modified. The claims are further directed to a method of delivering a peptide to the nucleus of a cell, particularly an insect cell.

First, with respect to the term "modified", since baculoviruses (and their coding sequences) are naturally occurring it is not apparent what is represented by a starting baculovirus or baculovirus coding sequence and what it is modified to. Therefore, the term "modified" may be interpreted to read on any naturally occurring capsid (or capsid protein). Also, the following language of claims 1 and 6: "to display one or more heterologous peptides" or "to express one or more heterologous peptides in its capsid" is not given patentable weight for the purposes of the instant rejection as such language appears to be an intent as opposed to a functional characteristic of the baculovirus.

Liu et al taught that genes encoding capsid protein vp39 from Chinese and Japanese isolates of bombyx mori nucleopolyhedroviruses share 97.5% homology while the protein products of the genes share 97.1% homology. Liu et al further taught that the vp39 gene of the Chinese isolate is nine nucleotides longer the vp39 gene of the Japanese isolate. Also, Liu et al reported that vp39 from the Chinese isolate comprises amino acid substitutions, as compared to vp39 from the Japanese isolate, which resulted in a modified secondary structure. See the abstract. Liu et al also taught transduction of Sf9 insect cells with the Chinese baculovirus isolate, which reads on delivery of a peptide to the nucleus of a cell, particularly an insect cell. See figure 2 on

page 158. Finally, claim 7 is anticipated as the baculoviruses of Liu et al comprise more than three genes, particularly because the claim does not specify if the genes are viral or non-viral. Therefore, given the claim interpretations as discussed above, the Chinese baculovirus isolate of Liu et al represents a baculovirus having a modified capsid or a modified genome (modified in the sense that the sequence is different from that of the Japanese isolate), wherein the gene encoding capsid protein vp39 is modified.

Thus, the teachings of Liu et al anticipate all of the instant claim limitations.

Claims 6-7, 9-10 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Loo et al (Journal of Virology, 2001, 75(2): 961-970; IDS).

The claims are directed to a baculovirus having a modified genome and comprising a human gene. The claims are further directed to a method for delivering a peptide into the nucleus of a cell, wherein the cell is a mammalian cell.

The following language of claim 6: "to express one or more heterologous peptides in its capsid" is not given patentable weight for the purposes of the instant rejection as such language appears to be an intent as opposed to a functional characteristic of the baculovirus.

Van Loo et al taught a baculovirus whose genome comprises a humanized green fluorescent protein (gfp-bac), which is interpreted to read on a human gene. See page 962, in column 1, in the material and methods section as well as at page 963, in column 1. Liu et al also taught infection of human cells with the gfp-bac, which is interpreted read on delivery of a peptide to the nucleus of a cell, particularly a human cell. See

page 963. Therefore, given the claim interpretations as discussed above, the gfp-bac of van Loo represents a baculovirus having a modified genome. Finally, claim 7 is anticipated as the gfp-bac of van-Loo et al comprise more than three genes, particularly because the claim does not specify if the genes are viral or non-viral.

Thus, the teachings of van Loo anticipate all of the instant claim limitations.

Conclusion

No claim is allowed. Claims 8 and 13 appear to be free of the prior art of record but are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Paras, Jr. whose telephone number is 571-272-4517. The examiner can normally be reached on M-Th, 7-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (571) 272-0532.

Peter Paras, Jr.

Art Unit 1632

PETER PARAS, JR.
PRIMARY EXAMINER